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Physiological Plasticity and Brain Circuit Theory

The standard Sherringtonian picture of central nervous integration has not received universal acceptance. Students of behavior, in particular, have on numerous occasions expressed dissatisfaction with the conventional fiber circuit concepts. They argue that the central switchboard analogies and reflex circuit diagrams of classical neurology may be all right for the anesthetized and spinal preparations, but that they are hardly adequate to account for the tremendous plasticity and the amazing purposive adaptibility of the normal intact animal. Other objections to conventional circuit theory with direct experimental foundation attained substantial proportions during the twenties and thirties. Outstanding were those that stemmed from brain lesion studies demonstrating the ability of the brain to approximate normal function in the face of extensive cerebral damage. Cortical lesions produced initially in the expectation that whole blocks of memory and categories of experience and behavior would be wiped out proved in many cases to have so slight an effect on functional organization and memory as to tax the ingenuity of the investigator to detect any behavioral deficits. The question of the locus and nature of the memory trace or engram became recognized, through the work of Lashley (13), in particular, as one of the most baffling of all neurological problems. Almost any engram scheme that might be expressed within the framework of the traditional approach to cerebral integration, i.e., in terms of specific fiber connections, seemed to be ruled out.

The case against the conventional connectivist approach was supported further by numerous clinical and experimental observations on nerve crossing and muscle transplantation which seemed to indicate a complete functional interchangeability of neuronal connections, undermining thereby the basic thesis that functional specificity depends on differential fiber connections. Additional objections arose out of the widespread demonstrations of Gestalt principles in perception, principles that emphasized the importance of the whole pattern in brain excitation and at the same time ruled out functional specificity among the neuronal elements. Concomitantly, a series of studies on the puzzling phenomenon of homologous response (50) and its various ramifications seemed also

to rule out differential connectivity as a basis of integration, pointing to some kind of resonance principle as an alternative.

Bolstered by the foregoing and other lines of evidence, the anti-connectivity movement had become strong and was gaining rapidly by the late thirties. On the other hand, such constructive suggestions for brain theory as had emerged from the separate lines of evidence remained diverse and inconsistent. In each case the new hypotheses accounted satisfactorily for one or for a few of the plasticity phenomena on which they were directly based, but they remained inadequate with respect to others. In the following I shall attempt to consider, one at a time, some of the more substantial and impressive lines of evidence and related arguments that have been advanced against orthodox reflexology, i.e., the evidence and arguments that have seemed to be the most convincing and demanding of some answer or explanation.

RE-EDUCATION AFTER NERVE CROSSING AND MUSCLE TRANSPOSITION

Many kinds of nerve cross-union and muscle transplantation have been described in the early literature (2, 3, 7) with statements that they lead to complete functional readaptation. Readjustments in the hind limbs were reported to survive spinal transection, implying a type of spinal learning and a basic plasticity in some of the most primitive and supposedly most fixed pathways of the neuraxis. Many investigators emphasized that these readjustments occur immediately and spontaneously with no necessity for any relearning. From these latter, especially, the conclusion was drawn that central coördination mechanisms are independent of any exact morphology in neuronal connections, and that we must therefore seek some entirely new principles of integration, quite different from those envisaged by Sherrington and his followers.

Some fifteen years ago it seemed that a good approach to problems concerning the brain engram and functional plasticity in general might be made through an analysis of the neural changes underlying readjustments of this type. The central nervous changes involved promised to be relatively simple, direct, and circumscribed compared with those for the maze, problem box, and perceptual discrimination habits previously studied. By combining cord and brain transections at various levels with cortical lesions and electric stimulation and recording, it looked as though one ought to be able to pin point the location, and perhaps determine something about the nature, of the underlying neural changes.

When we embarked on this project, our efforts were thwarted from the start by the repeated inability of our animals to effect any significant

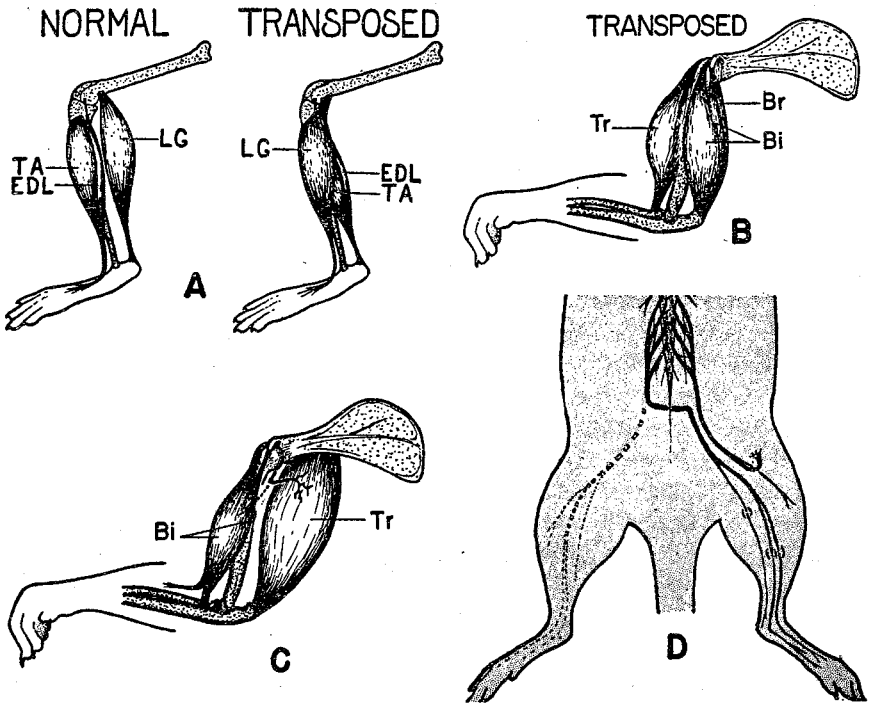

Fig. 119.—Some nerve-end organ disarrangements which have produced in rats corresponding sensory and motor dysfunction that remained uncorrected by re-education. *A*. Transposition of opposing flexor and extensor muscles of hind limb (25, 26). *B*. Same in forelimb (27). *C*. Reinnervation of triceps extensor muscle by antagonist nerve from biceps flexor muscle (27). *D*. Contralateral crossed innervation of right foot by nerves from left foot (28).

central reorganization in response to the surgical alterations produced in the periphery. The rearrangement of nerve-end organ connections resulted repeatedly in corresponding functional disorder that tended to persist indefinitely with little or no correction by re-education. For example, rats with flexor and extensor nerves of the leg interchanged, or with the corresponding muscles transposed as early as the third week after birth (Fig. 119), would go through the remainder of their lives making all movements of the affected foot in reverse (26). Monkeys with the nerve supply of the brachial biceps and triceps muscles interchanged learned quickly to inhibit the resultant reversal of elbow movement, but failed in a period of three years to effect any generalized positive correction of the reversed muscle action (35). After sensory nerves had been crossed in rats from the left to the right leg, the development of painful

trophic sores on the sole of the reinnervated right foot in some of the animals caused them to hop about on three legs, bearing extra weight on the inflamed right foot in order to hold up protectively the uninjured left leg. This maladaptive behavior continued uncorrected throughout the waking day for six to nine weeks until the aggravated ulcers eventually healed. In one case the reflex rigidity was fatal (28). Frogs, newts, and fishes with their eyes surgically rotated 180 degrees responded thereafter as if the visual field had the illusory appearance of being upside down (29, 31, 37). Application of conditioning techniques and other special training measures failed to bring about readaption of these and similar types of functional disorder.

A critical revaluation of the older studies undertaken in the light of these contradictory results disclosed that in nearly all cases the earlier optimistic interpretations were suspect (32). In many instances, it is quite obvious that other factors such as vicarious muscle function, anomalous innervation, two-joint tendon action and the like, were mistaken for reorganization in the central circuits of the nerves involved. Although the evidence indicates that some reorganization is possible, particularly with respect to muscle transposition in man, it is definitely restricted and appears not to exceed that achieved in other types of sensory and motor learning.

In brief, the earlier counterindications for traditional connectivity theory are now superseded by data leading to a much more conservative estimate of central nervous plasticity. Instead of demanding new mechanisms of integration as seemed originally to be the case, the nerve cross and muscle transplantation data have now backfired and offer instead strong support for the old idea that specificity of function is closely associated with specificity in the morphology of nerve fiber connections.

MYOTYPIC (HOMOLOGOUS) RESPONSE AND RESONANCE

One exception among the foregoing remained unaccounted for. This was the observation that disarrangement of nerve-muscle connections in the limbs of larval amphibians fails to produce any corresponding functional disorder. In a series of investigations beginning in 1922 Weiss (49, 50) had shown that muscle coördination undergoes an orderly recovery following various kinds of surgical alterations in the normal innervation pattern. More recent experiments, published in part, have revealed the same type of motor recovery in adult *Triturus,* the water newt, and in the fin and trigeminal musculature of the adults of several species of fishes (38, 45). Adult toads and frogs, on the other hand, are incapable of the same kind of recovery (50), and it has been found to fail also in the oculomotor system of amphibians, and certain fishes (33, 45).

The studies by Weiss had demonstrated that this "myotypic" form of motor recovery can be obtained under conditions that clearly eliminate any kind of relearning process or reflex form of readjustment. The results seemed entirely incompatible with the idea that spinal reflex integration is based on specific fiber connections. As an alternative it was proposed that each muscle acts like a resonator responding selectively to a particular frequency of discharge, and that all frequencies are emitted over all the muscle nerves. On this basis it would make no difference to which nerve a given muscle is connected.

This form of the hypothesis was disproved in 1931 by Wiersma (52) with electric recording methods. Wiersma then modified the original interpretation with the suggestion that the muscles impose their specific resonance properties on the motoneurons such that the entire motor unit, rather than just a muscle, acts as the resonator. This modification of the resonance theory has survived to the present. The change in the motoneuron induced by a foreign muscle is called "modulation." Meanwhile the idea that frequency of discharge is the basis for the selective central activation has given way to the notion of qualitatively distinct modes of central excitation, a specific mode for each muscle of the limb (50, 51).

When we tried to reconcile this interpretation with the conflicting results in mammals mentioned above, it became apparent that most aspects of the myotypic response phenomena could be accounted for if one assumed that alteration of the peripheral connections of a motoneuron somehow leads to a compensatory switch in its synaptic relations within the centers (26). The influence of the muscle on its motoneuron as conceived by Wiersma and Weiss could be interpreted as having its direct effect, not on selective receptivity to specific modes or frequencies of central excitation, but on selective tolerance for specific types of synaptic end-feet. Specific chemical affinites between the motoneurons and the different classes of central fibers, might then account for the selective synaptic contacts. Regeneration of a motor axon into a new muscle could be conceived to cause some kind of trophic breakdown in the synaptic end-feet on that motoneuron to be followed by the formation of new end-feet from other fibers having the proper chemical affinity. Such an hypothesis would explain the recovery of normal motor coödination with abnormal nerve-muscle connections. The lack of similar recovery in the rat and other mammals could be ascribed to an early loss in mammals of the embryonic plasticity required for such tissue breakdown and respecification.

Such an explanation had the advantage of not requiring any drastic revision of established neurophysiological principles. Furthermore, it seemed likely that the same factors would be operating under the conditions of normal development to insure the initial establishment of proper

reflex relations. If so, one would have here the basis for a general theory of the developmental patterning of synaptic end-feet, a theory to replace older explanations that were based on neurobiotaxis (12) and had leaned heavily on function and experience to account for the developmental organization of the nerve centers.

Such a reinterpretation was in conflict at first with the prevailing view of the thirties that the regeneration and termination of nerve fibers is nonselective and that the central nervous system is incapable of functional regeneration on the scale required. Subsequent investigation has since shown that the central nervous system of amphibians and fishes has extensive regenerative capacity even in the adult. Full functional recovery has been observed after regeneration of the transected midbrain, spinal cord, optic nerve, and vestibular, trigeminal, and dorsal spinal nerve roots. The recovery, furthermore, is always of an orderly type, suggesting a strictly selective re-establishment of synaptic terminals (23, 39, 40). There has not as yet been any direct morphological demonstration of the inferred selective synapsis, however, and the issue remains unresolved to the present. The connectivity interpretation is favored by the broad background of neurological data that has led to the general discard of specific nerve energy and resonance concepts in favor of selective synaptic relations as a basis for central integration.

CHEMOAFFINITY IN THE PATTERNING OF NEURONAL CONNECTIONS

The general picture of the developmental patterning of neural circuits in terms of selective chemoaffinities becomes increasingly credible. Supporting evidence has been extended to include synaptic patterning in the visual, vestibular, and cutaneous pathways, and in the central tectobulbar, tectospinal, and associated mesencephalic and spinal fiber tracts (see Fig. 120). The consistent results suggest general application to the entire nervous system. Since the general scheme and supporting evidence have recently been presented in some detail elsewhere (39, 40, 43), only the broad outlines are mentioned below.

Essentially the hypothesis supposes that the neuron population undergoes an extremely refined embryonic differentiation somewhat as follows: After the embryonic cells for the nervous system have been separated from those for muscle, bone, cartilage, etc., the neuroblasts continue to differentiate among themselves. At first the differentiations are broad: into motor and sensory systems, cephalic and spinal, brachial and thoracic. Later within these groups subgroups are formed, and differentiation continues, producing greater and greater refinement and complexity. Even-

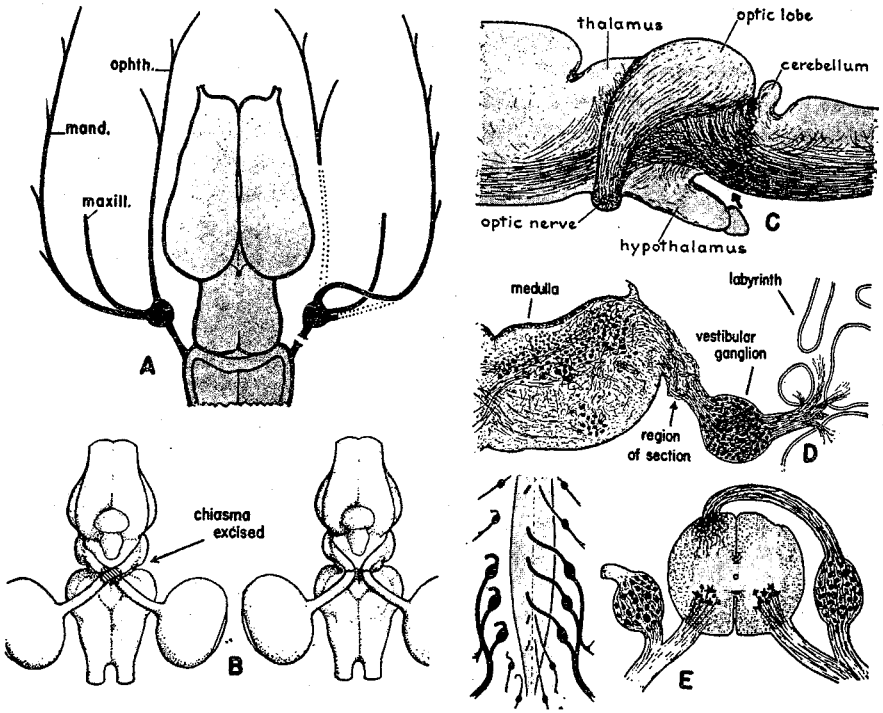

Fig. 120.—Regeneration of central synaptic connections in the following and similar situations is found to effect an orderly re-establishment of reflex functions: *A*. Regeneration of divided trigeminal nerve root, with peripheral cross-union of ophthalamic and mandibular nerves (39). *B*. Regeneration of divided optic nerves into wrong side of brain (39). *C*. Regeneration of sectioned mesencephalic fiber tracts with eyes rotated 180 degrees (36). *D*. Regeneration of divided vestibular nerve root with optic nerve resected (39). *E*. Regeneration of crossed sensory roots of hind limb (40).

tually the primary motor neurons become stamped with additional specificity by the muscles they innervate. Similarly, the primary sensory neurons, after being divided into different classes for the different modalities of sensibility, are further specified within each sense modality to mediate various local sign properties as in the retina, cochlea, skin, tendons, joints, etc. An equally refined and even more complicated differentiation must take place concurrently and in the later stages among the association neurons in the centers. The final specificity of the neuron is determined in many cases by inductive effects transmitted through terminal contacts from other neurons and end organs.

Once the qualitative individuation of the nerve cell population is achieved, it becomes possible for selective interconnections to be made

between different classes of neurons on the basis of specific chemical affinities. The fact that the particular patterns of chemoaffinity produced in ontogeny happen to result in circuit connections that are functionally adaptive may be ascribed to evolutionary selection. The developmental mechanisms directly responsible in ontogeny remain largely obscure although some of the broader principles of the developmental process are becoming clear. Organizer and inductor effects, embryonic fields, self-differentiation, potentiation, and most of the other basic concepts developed in experimental embryology seem to have application in the patterning of the neural circuits. According to this view, the final prefunctional patterning of precise synaptic relations merely involves a refinement of developmental and cytologic mechanisms long recognized in grosser form in other phases of ontogeny. From the embryological standpoint, the chemoaffinity concept of the developmental patterning and maintenance of synaptic connections brings the ontogeny of inherited behavior mechanisms into line with the development of other organ systems.

Like most developmental processes, the specification of nerve cells exhibits adaptive plasticity and reversibility in early stages. Only in later stages of development does the specificity tend to become fixed and irreversible. If surgical alterations are performed during the early plastic period, embryonic adjustments leading to functional readaptation ensue. In the fishes and amphibians neuronal specificity remains plastic for long periods, even into adult stages. This is paralleled by other evidences of tissue plasticity in these forms such as the ability to regenerate limbs, fins, and tails, the lens of the eye, the retina and optic nerve, and central nervous fiber tracts. Most of the phenomena of neural readaptation following surgical alterations in the lower vertebrates are to be understood in these terms. The plasticity is one of embryonic development rather than of neural function.

The selectivity of staining reactions in different parts of the nervous system and the selectivity of drug action, of toxicity effects, of bacterial and viral invasion, of the incidence of degeneration, and the like are all indicative of chemical differentiation generally at a much more crude level than that involved in the patterning of synaptic relations. With regard to future possibilities for specific chemotherapy in nervous and mental disease the above picture of refined chemical differentiation among the neural centers is an encouraging one. That the elaborate qualitative specificity within the neuron population has utility, beyond the establishment and maintenance of synaptic relations, is suggested in the direct response of certain nuclei to different blood constituents. What further direct role it may play in integration remains to be determined.

In summary, it is possible in these terms to account for myotypic response and related phenomena without departing from orthodox connectivity principles. The data have extended further the evidence for the existence of a high degree of qualitative, presumably chemical, specificity among nerve cells correlated closely with the inherent functional differentiation. The results further emphasize that in lower vertebrates, at least, the basic features of space perception, including retinal, vestibular, and cutaneous local sign, and position sense as well as the basic elements of motor coördination and of other functions at reflex and higher levels, are built into the nerve centers under genetic control and are not subject to major reorganization through experience and training. Finally, the findings support a plausible working picture, outlined elsewhere (40, 43), of the way in which these inherited features of neural organization can be organized prefunctionally in the growth process itself.

ELECTRIC FIELD THEORY

The electric field hypothesis of cerebral integration proposes a revision in neurological theory which, if substantiated, would invalidate many of the traditional concepts of brain organization based on orthodox fiber-conduction principles. Proponents of electric field theory hold that a major role in cerebral organization is played by mass electric currents flowing through the cortex as a volume conductor. The subjective aspects of perception are thought to be more satisfactorily correlated with these gross electric currents in the brain than with the orthodox type nerve impulses traveling in discontinuous scattered patterns along discrete fiber pathways. Field theory also purports to account more readily than the fiber circuit schemes for various Gestalt and other relational effects in behavior, particularly in the area of perception.

A partial test of the electric field hypothesis was attempted some years ago in an experiment (34) designed to determine the importance in cerebral organization of horizontal or tangential intracortical conduction over the horizontal fiber systems of the cortex. Numerous subpial knife cuts were made in crisscross patterns throughout the sensorimotor cortex in the monkey (Plate 28). The cuts, extending radially through the depth of the gray matter, would have blocked any tangential intracortical conduction over distances of the kind required to mediate relational interaction between motor and sensory points for different joints of the limb. Presumably the walls of clotted blood and subsequent scar tissue should also have deformed any precise normal patterning of direct-current flow within the subdivided area. Nevertheless, almost no functional disorganization resulted from this extensive cortical parcellation.

A subsequent effort to distort the postulated cortical currents of field theory by short-circuiting them with metallic inserts (16) also failed to produce visual disturbances. From the standpoint of field theorists, however, this first short-circuiting experiment was considered inconclusive because the functional tests had been quite simple and the metallic inserts had left unaffected large portions of the visual cortex corresponding to nearly a quadrant of the visual field. When these were remedied in comparable experiments on the cat (47), there was again no significant functional disturbance. Further, the application of the subpial slicing procedure to the cats' visual cortex (47) similarly failed to disrupt refined visual pattern discriminations (see Plate 28).

Objections that the mass cortical currents might pass undistorted through the above knife cuts and also around the metallic inserts seems to have been answered in a later investigation (46). In this case a large number of small dielectric plates of mica were inserted all through the visual areas of both hemispheres, as illustrated in Figure 122. The object again was to distort, by blocking instead of by shorting, the postulated mass electric currents of visual form perception. In spite of the cortical damage inevitably produced by such inserts, the functional effects again were hardly measurable where the inserts were confined to the depth of the cortex. When the mica plates were pushed deep into the white matter, pronounced visual impairment ensued, but this was followed by recovery of a fair to high level of pattern recognition in the course of two and one-half months. The functional deficits produced by the mica inserts were no greater than those produced by control knife-cut lesions that simulated the tissue damage produced by the inserts.

One can find little justification in the results of this series of investigations for continuing to approach the problems of cerebral function in terms of the electric field theory as it is currently formulated. This conclusion is supported also by considerations of a more theoretical nature (16, 41) that have seemed from the beginning to favor the classic fiber conduction doctrine. Certain other theoretical proposals for cortical integration based on "transcortical irradiation," "scanning in random networks," and "reduplication of interference patterns" are equally difficult to reconcile with the above findings.

SECTION OF CEREBRAL FIBER TRACTS

Deep knife cuts that invade the white matter of the hemispheres to interrupt large bundles of association fibers between cortical areas have been reported to produce amazingly little or no defect in the learning and retention of maze and other trained habits in rats, dogs, and monkeys (15,

53). Perhaps the most dramatic of such findings is the observation that the entire corpus callosum, the largest fiber tract of the brain by many times, can be completely sectioned in man without producing any clear-cut functional symptoms, either overt or introspective. Piano playing, typing, tap dancing, contralateral transfer of learning in mirror drawing and in nonvisual stylus maze tasks, binocular depth perception, and apparent movement across the vertical mid-line of the visual field have all been studied (1, 4, 24) and reported to be unimpaired to any significant degree by callosal section. Such findings are difficult to reconcile with the idea that intercortical fiber connections are basic to cerebral integration. The results on man in particular have been taken as evidence of the need for an entirely new approach to cortical physiology and the neural basis of learning.

The evidence on cerebral tract section does not all point in the same direction. In our own experience, the surgical invasion of the white matter in cats and monkeys causes much more pronounced functional impairment than do comparable lesions restricted to the gray matter (34, 46, 47). Maspes (17) used tachistoscopic tests on patients with callosal section and found that visual patterns such as letters, numbers, geometric figures, and the like were seen but not comprehended when projected to the nondominant hemisphere in two patients with callosal section. Alexia and tactile agnosia on the nondominant side were mentioned also by Dandy (6). Section of the callosum in dogs is said to prevent the usual transfer of cutaneous conditioned reflexes to contralateral homologous areas (5).

Recent investigations by Myers (22) show that the corpus callosum in the cat is essential for the contralateral transfer of visual learning and memory from one hemisphere to the other. The visual input in these experiments is restricted to one hemisphere by mid-line section of the optic chiasma (Fig. 121) and by placing a blinder over one eye during the training and testing. Under these conditions, it is found that visual discriminations learned with one eye can be performed readily with the untrained eye. This interocular transfer fails, however, with the callosum sectioned. In fact, with the callosum divided, completely opposing and otherwise incompatible discriminations can be trained through the separate eyes with no interference (21). A discrimination task that has already been learned and overtrained with one eye requires as long to relearn with the second eye in chiasma-callosum sectioned cats as if it had never been seen before (48). These animals have no recollection with one eye of what they have been doing with the other eye.

Results of the same kind have been obtained in the tactile sphere. Discriminations for roughness, hardness, and shape learned with one forepaw are found to transfer at a high level to the contralateral untrained paw

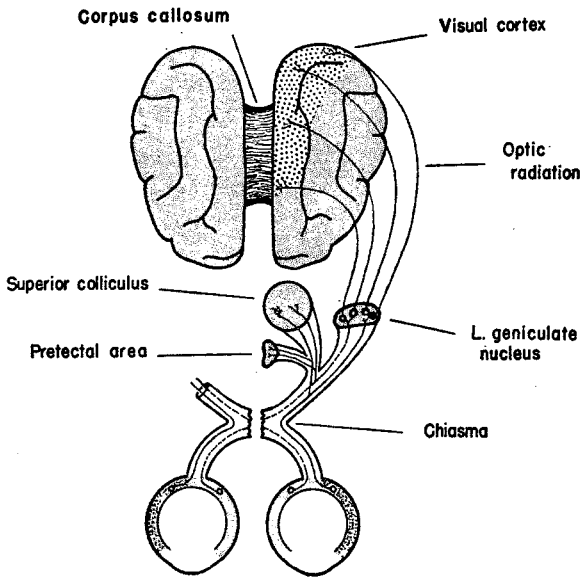

Fig. 121.—After midsagittal section of optic chiasma, visual discrimination habits learned with one eye transfer readily in cats to the untrained eye provided posterior portion of corpus callosum is intact (22). If the callosum is sectioned also, such interocular transfer is completely absent (21, 48).

in normal cats, but in cats with the callosum sectioned, such contralateral transfer fails, and the discrimination has to be relearned from the beginning with the second paw (Stamm and Sperry, unpublished). Even the initial adaptation to the training apparatus, which involved learning to push one of two pedals in the proper manner, and which thus was largely motor, had to be retrained when the cats were shifted to using the second paw.

Perceptual learning and memory seem thus to proceed quite independently in the two hemispheres in the absence of the callosum. It is interesting that in spite of this independence, the learning curves of the two separated hemispheres are strikingly similar in character in the same individual though they differ in the usual way from animal to animal and from problem to problem in the same animal. We have found this to be true both for visual (48) and for tactile discrimination (Stamm & Sperry, unpublished) The fact that the individual variability in perceptual learning runs parallel in the two separated hemispheres indicates that this variability is less a matter of accident and of fortuitous events in the

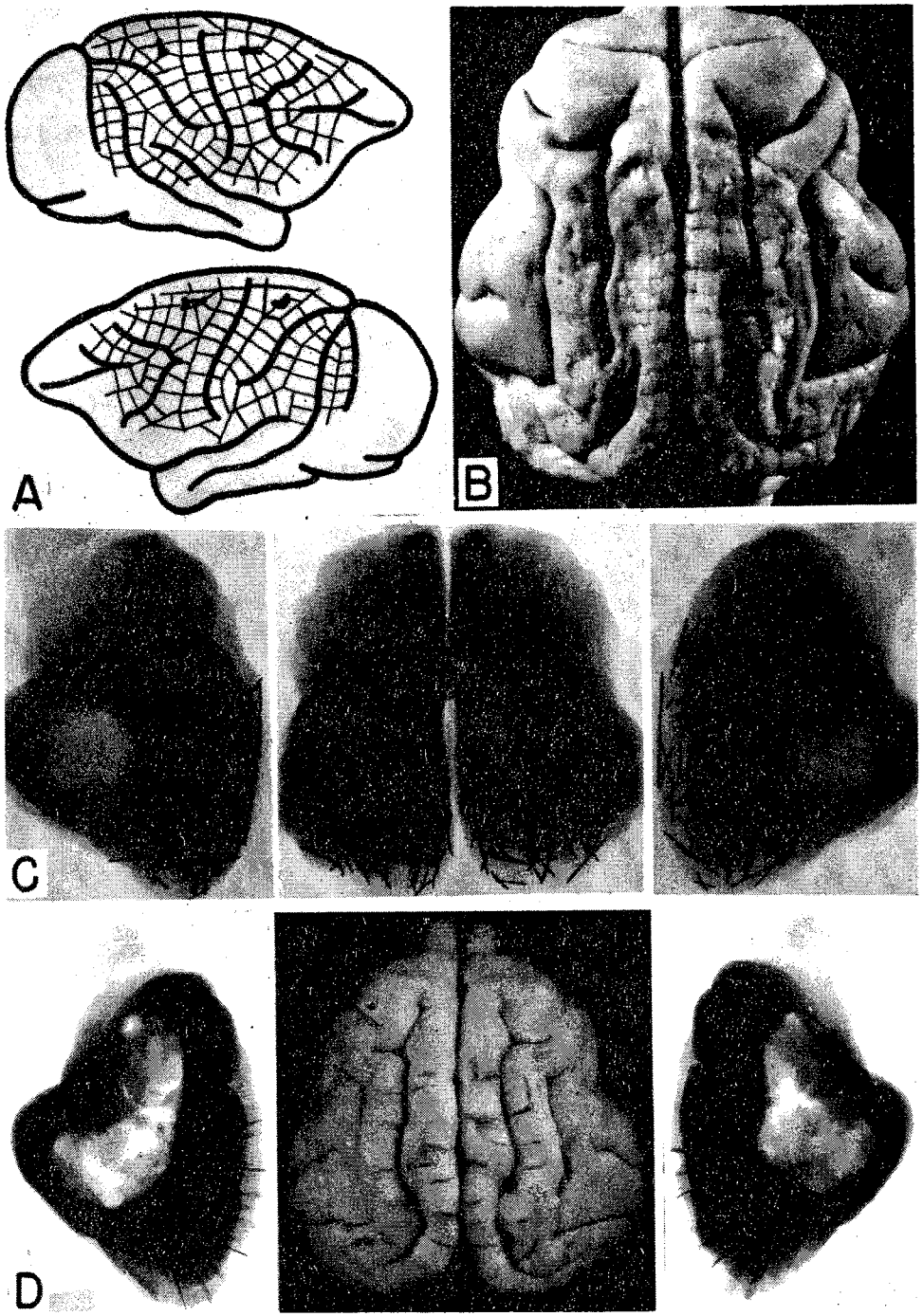

Plate 28.—Failure of the above types of cortical insult to produce major functional disruption is difficult to reconcile with electrical field theory and with any hypothesis based on tangential intracortical conduction. *A*. Multiple subpial knife cuts in sensorimotor cortex of monkey (34). *B*. Same in visual cortex of cat (47). *C*. Lateral and dorsal X-ray views of tantalum wire insertions in visual cortex of cat (47). *D*. Lateral

learning process and general training situation than one might have supposed. It appears to be predetermined to a surprising degree by the intrinsic structural and functional organization of the cerebral hemispheres. To what extent this organization is acquired and to what extent inherited remains to be determined.

The studies on callosal section in the cat at least indicate that this structure has an important role in integrating the activity of the two hemispheres. It would appear to follow that a learning task that involves a bilateral influx of learning cues ought to be mastered more rapidly with callosal function intact. To what extent the individual fibers have specific function remains to be determined. Preliminary results of Myers suggest that in the cat transfer of simple visual discriminations can be effected following section of all but a small segment of the callosum about 2 mm. long and that it is not critical which small segment is left so long as it is in the posterior half.

The studies on callosal function show consistently that easily learned discriminations transfer more readily than difficult ones, and that the learning is more rapid and stable on the trained side than on the contralateral side. If there is interference or conflict in one hemisphere between a habit directly trained and one transferred from the other side, the direct training effects are strongly dominant over the transfer effects, other things being equal (22). One gets generalization effects in callosal transfer as in normal learning. If, however, two related patterns are differentiated on one side by long training, the differentiation tends not to transfer although the individual discriminations and generalization effects do so readily (Myers and Sperry, unpublished). We have recently seen this same monocular differentiation fail to transfer to the untrained eye after section of one optic tract, i.e., the differentiation did not transfer from the crossed to the uncrossed fiber systems within the same hemisphere.

With regard to the problem of the localization of memory traces, it is interesting that transfer of visual learning through the callosum can be obtained after removal of the entire occipital, parietal, and temporal lobe cortex on the trained side (Myers and Sperry, unpublished). The cortical removals are made after the completion of training and before switching the blinder. The transfer is erratic under these conditions, occurring in some cases and not others, but the amount of cortex removed beyond the striate area does not seem to have much effect upon the degree of transfer. Easy discriminations transfer much better than difficult ones under these conditions. The same type of result has been obtained (21) when the callosum is sectioned after training is completed and prior to the testing

for transfer. The results demonstrate that the memory traces or engrams for these perceptual habits are not confined to the directly trained, receptive area of the cortex. In some form or other they get across to the opposite side. Transfer of a simple but not a difficult discrimination has been observed after removal of the anterior half of the visual cortex of one hemisphere and the posterior half of the other, suggesting that these transfers through the callosum are not just simple mirror images of the sensory input.

It would appear that the callosum operates primarily in the highest-level activities where learning and memory are involved, but is not critical for more basic sensory and motor integration. This is consistent with the recency of its phylogenetic evolution and with the fact that complete section fails to produce any direct symptoms apparent to casual observation.

FUNCTIONAL PLASTICITY THROUGH DIFFERENTIAL PATTERNING OF FACILITATION

Some of the most convincing arguments and bodies of evidence advanced against conventional connectivity theory have failed in the last decade to withstand critical examination and experimental test. The outcome has done more than reflect doubt on the new hypotheses. In a number of respects we have emerged with positive evidence of the direct dependence of normal function upon specific nerve connections. The results favor adherence to traditional circuit theory with allowance for amplifications and revisions where necessary, rather than continued search for some radically new mechanism of integration.

This means that eventually one must be able to find satisfactory connectivity explanations for various other phenomena that heretofore have made the classical theory appear inadequate, i.e., such phenomena as sensory and motor equivalencies, response reversals, equipotentiality and vicarious function of cortical areas, size and shape constancies, perceptual generalization, abstraction, and the like. These and many other forms of functional plasticity will require separate and specific analysis before one can expect any satisfactory understanding. An important advance toward reconciling some of these phenomena with fiber circuit theory has already been made by Hebb (11). I shall only try here to take one more step in the same direction by pointing out the rather general and paramount role that facilitory sets may play in the mediation of much of the plasticity in neural integration.

With facilitory sets operating in a switchboard or fiber circuit system, the functional patterns, though still dependent on specific connections,

become much less a direct reflection of the underlying structural design. Given a morphologically rigid circuit system of sufficient complexity, it is possible, for example, to get an almost unlimited variety of different responses from the same invariant stimulus simply by shifting the distribution of central facilitation, i.e., by opening certain central and motor pathways at one time and others at another time. This can be illustrated in simple form at the spinal level. If a spinal salamander is tapped on the tail, the hind leg will respond by retraction or, conversely, by protraction, depending on which of the spinal limb centers happens to be in a state of facilitation and which in a state of inhibition (8). These central states are proprioceptively controlled by the posture of the limb.

The same principle has much wider application at the cerebral level. This can be illustrated with reference to the common voluntary reaction-time experiment: A subject is told to respond as quickly as possible at a certain signal by pushing a key with the finger. When the subject is set for this response, the proper signal triggers off an immediate depression of the key with the short latency of approximately 0.25 sec. However, the same signal may evoke just as rapidly the opposite response if the subject is instructed to pull the key instead of pushing it. Or, the response may be similarly changed to a movement of the foot or of the vocal apparatus without significant increase in latency. By means of fleeting shifts in the central patterns of facilitation and inhibition the same signal can be linked directly to any one of literally hundreds of different responses. No change in brain morphology, no alteration of its wiring plan, is required.

The brain circuits are so constructed that numerous alternative pathways of discharge are available at each integrating center. However, only one or a few of the potential patterns of discharge are open (facilitated) at any one time, the others being closed by inhibitory activity. By this opening and closing of different patterns of circuits at different times, the single morphological network can in effect be transformed into many different types of circuits with widely differing properties and capacities. A very large part of the plasticity and versatility of the nervous system seems to be based on just this principle.

Like a computing machine the neural mechanism can be preset to respond to a given series of numbers by addition, subtraction, or multiplication. Unlike any computors available to date, the same neural mechanism can also be preset at different times for running or walking, typing or piano playing, conversing in French or in Spanish, recording objects by color or by form or by both, and so on and on. By virtue of these different settings, the neural machine becomes many machines in one. We urgently need further analysis and understanding of these differential facil-

atory sets, how they are controlled, and the principles on which they operate. Possibly some of the recent work on interrelations between cortex and brain stem discussed by Dr. Jasper and Dr. Magoun in this Symposium may lead in this direction.

It might be mentioned in passing that any calculations of the limit of the nervous system's capacity for absorbing and producing information must be made in terms of these multiple settings. When these are taken into account, the full capacity of the brain is infinitely extended beyond the total number of combinations and permutations of cellular and fiber interconnections. In fact, an entirely different formulation of the problem is indicated. On the proposed terms neither the subjective information nor its neural basis is necessarily restricted to any number of "bits," i.e., it is not necessarily quantized at all, but may involve all manner of continuous shades, and intergradations.

With regard to the total brain organization and its enormous efficiency, one could say that the inhibitory aspect of the facilitory set is perhaps even more important than the excitatory. If the hind leg of the decerebrate salamander is placed in an extreme position of protraction, thus facilitating the spinal centers for retraction, all other possible responses, e.g., protraction, adduction, abduction, inversion, eversion, and intermediate combinations are inhibited. Similarly, if the cerebral mechanisms are set for a specific activity, such as card sorting, all the thousands of other activities that might equally well be carried out in the same situation, but which are incompatible with the sorting process, are automatically excluded. Normally the brain does not get confused by activating mixtures of the thousands of settings at its command. Each setting somehow inhibits all other inappropriate excitation patterns.

One can think of the functional settings of the brain as being related to one another in tree-like fashion, each with the same central trunk, but each with an almost infinite array of possible distal ramifications. The motor set for the reaction time experiment, for example, may have subordinate branches, so to say, for movements of the hand or the foot and each of these members further can be preset for movement in a theoretically unlimited number of directions from any given starting posture. Another main branch for movements of the vocal apparatus can be preset to respond with any one of as many different words, phrases, and nonsense syllables as exist in however many languages the subject knows. Perhaps it would be more accurate and fruitful to picture the differentiation and interrelations of facilitory sets, not in terms of tree limbs and branches, but directly in terms of the potential postures and movements of the vertebrate body. The "postural sets" then have direct application to overt movement and, perhaps, more or less direct implication for the implicit

operations of perception and thought processes, depending on the closeness or remoteness of these latter to motor adjustment.

MORPHOLOGICAL OVERLAP AND FUNCTIONAL REINFORCEMENT

The physiological reinforcement obtained through overlap in fiber terminations is an important stabilizing factor in function, particularly in the preservation of organized activity after extensive nerve lesions. This principle is nicely illustrated in some experiments of Gray and Lissman (9, 10): If all the dorsal sensory roots of the spinal cord are transected in the adult toad, all walking is abolished. However, if only one, or to be safe, just two roots are left intact, it does not matter which two, the ambulatory pattern can still be evoked with all four limbs moving in the proper diagonal sequence. After more than two limbs are deafferented there begins a progressive loss of ambulatory coördination that increases with advancing stages of deafferentation. However, reminiscent of cortical mass action, it is the extent and not the site of deafferentation that is important.

By cutting the sensory and motor roots in various combinations, they found that the sensory feedback from any one limb helps to control the direction and timing of movement in all four limbs. This is true during each changing phase of the movement cycle of each limb. In addition there is feedback from the proprioceptors of the trunk that also reinforces the proper pattern of leg and trunk movement. Thus, the walking pattern of the entire trunk and four limbs tends to be reinforced as a whole from the separate movements of all the separate parts. The individual sensory roots transmit specific discharge patterns that spread through the full length of the cord on both sides. This tremendous overlap makes it possible to remove large fractions of the sensory input before the organization begins to fall apart.

We lack similarly clear evidence of this kind of thing in the higher centers. However, it is entirely conceivable that something of the sort is in part responsible for the fact that such large amounts of cortical tissue must often be removed to produce dysfunction and that in some situations it appears to be the quantity of cortex removed that counts regardless of its location. If multiple parts of a going cerebral excitation tend individually to reinforce all other parts and at the same time to inhibit incompatible patterns, many of the neural elements could be removed without destroying the organization of the whole. At least it becomes theoretically possible to account for much of the brain lesion data in these and related terms without relinquishing conventional fiber circuit concepts.

In this connection the brain lesion results also appear less embarrass-

ing for connectivity theory when one views the engram as a co-function of facilitory set, as recently outlined (42), reinforcing expectancies and related high-level phases of cerebral activity rather than direct sensori-motor or sensory-sensory associations. In these terms the engram, even for the simplest of conditioned responses, becomes relatively complex and diffusely distributed through the cortical apparatus.

INTRAHEMISPHERIC ASSOCIATIONS

Our experimental preoccupation with possible new approaches to the physiology of integration has, in one sense, merely led into a series of blind alleys. On the positive side, however, the results give new confidence in the connectivity approach and a conviction that one is not misled, after all, in continuing to search for specific functions in the various centers and connecting fiber systems of the brain, i.e., specific functions at the analytic, neuronal level, not at the level of molar behavior. Much disagreement in the past on questions of cerebral localization and functional specificity stems from a failure to specify the exact level of functional organization to which reference is being made.

It should perhaps be emphasized that there is nothing in the foregoing to detract from the possibility of qualitative differences among nerve impulses, particularly with reference to synaptic transmission. One would infer merely that any such specific nerve energy phenomena would have to be superimposed upon the basic connectivity mechanisms, adding functional refinement and differentiation, but nevertheless operating within the connectivity framework.

In recent efforts to learn more about connectivity principles in perceptual integration, we have been putting to use the demonstrated functional independence of the two hemispheres in what we have come to call the "split-brain" preparation. This is an animal in which the brain has been split down the middle by section of the corpus callosum, the optic chiasma, and usually also the anterior and hippocampal commissures. Such animals, incidently, are indistinguishable from normal to casual examination. The callosum appears to be necessary for the transfer of perceptual discrimination and memory from one hemisphere to the other, but in line with clinical observations, its complete section does not seem to impair immediate perceptual capacities or motor coördination.

In these split-brain animals one can leave intact a whole hemisphere to maintain generalized background functions and to prevent incapacitating paralyses. Cortical lesion and correlated methods of analysis can then be applied to specific learning and memory functions within the other single hemisphere. In the test hemisphere, instead of the customary

small lesions in the critical area, one can use the converse approach, i.e., the greater part of the cortex can be removed to leave intact only the critical area one wishes to test. The functional tests must of course be unilateral.

We have only begun to explore these possibilities in studies on the isolated visual and isolated somatic cortex in the cat. As an important first step in the investigation of perceptual integration, we have tried to determine the extent to which perceptual learning and memory can be mediated by sensory cortical area alone and to what extent it is dependent upon more complex integrations involving the function of other cortical areas. When an island of cortex including the area for central vision is isolated in the manner shown in Figure 122, nearly all previously trained

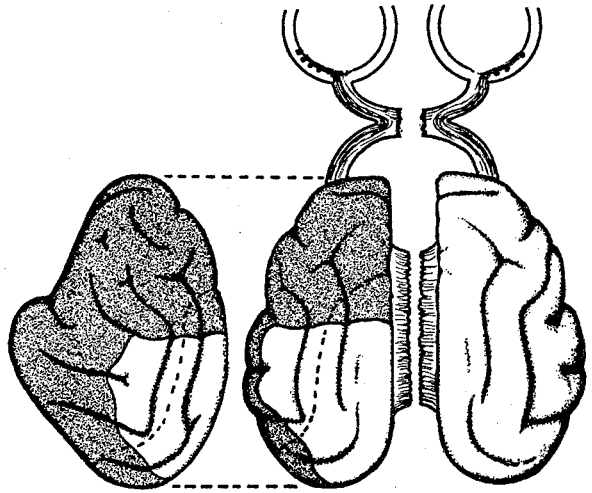

Fig. 122.—With chiasma and callosum sectioned as shown, isolation of left visual cortex in manner indicated severely impairs visual performance with corresponding (left) eye. Lateral tongue of cortex extending into auditory area is left intact to avoid damage to underlying optic radiation.

visual discriminations with the eye on the affected side are lost (Sperry and Myers, unpublished). The simplest discriminations, as between horizontal and vertical stripes, however, survive in the exceptional case and, if lost, can be retrained.

Preoperatively trained discriminations between a cross and a circle and between perfect and imperfect triangles can also be relearned by such animals, but the learning in the latter case fails to progress beyond the lower levels of our test scales for pattern discrimination (46). Preoper-

ative discriminations between upright and inverted **V**'s are lost and cannot be relearned. Such cats tend to bump into objects in walking about a strange room and may have difficulty locating a piece of meat held at close range in front of them. They work slowly in the testing apparatus and will run only about half as many trials as before the cortical removal. These impairments are not evident when the mask over the non-test eye is switched to the operated side or removed entirely.

Degeneration in the lateral geniculate nucleus in these cases is not sufficiently greater on the operated side than on the nonoperated side to account for the functional difference. That the visual impairment is not a result of geniculostriate damage is supported by the results of removing the nonvisual portions of the cortex in two stages. When the first removal includes the temporal lobe and all areas adjacent to the visual island, sparing only the frontal region with somatic sensory and motor areas, the deficit is less severe than if the somatic areas are included. Such animals show definite impairment in visual performance but retain most of their preoperatively trained discriminations at a fairly high level, including that for upright and inverted **V**'s. Subsequent removal of the remaining frontal region, which is too distant to involve the already isolated geniculostriate system, produces an additional marked and permanent lowering of visual performance to approximately the level obtained by making the total removal in one stage. It would thus appear that the somatic areas of the cortex play some important role in visual discrimination.

The results are different for somesthetic discrimination. In this case we are finding good retention of previously trained discriminations and good learning of new discriminations with the only remaining cortex

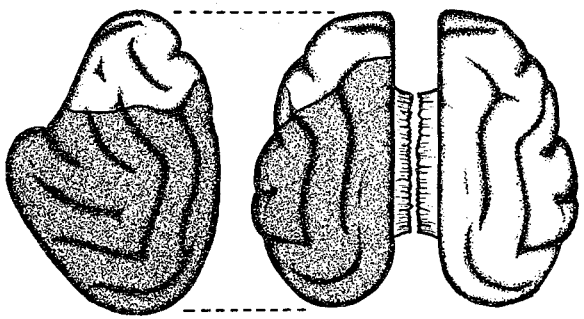

Fig. 123.—After isolation of small sector of left frontal cortex as shown, tactile discriminations with right forepaw are retained at high level and new ones are readily learned. Subsequent removal of remaining cortical island abolishes all discriminative performance with affected paw.

being the small amount shown in Figure 123 (Sperry and Stamm, unpublished). Apparently we are approaching a minimum here, because the most difficult discrimination task, involving choice between a smooth and a sandpaper surface, is not retained in the majority of cases and is relearned with difficulty. Also, an attempt to pare down the size of the remaining cortical island in one case so as to leave only the primary foreleg area, abolished all discriminative performance with the affected forepaw.

Possibly the greater functional efficiency of the isolated somatic cortex, as compared with that of the isolated visual cortex, can be attributed to the inclusion of the motor areas within the intact somesthetic island. At any rate, it would seem safe to infer that the cat is able to perceive, to some extent at least, with only a small island of cortex, and that widespread cortical integration is not essential for perceptual learning and memory. However, we are only just beginning to tangle with these latter problems and are in no position to foresee any definite answers.

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